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(54) Title: CALCILYTIC COMPOUNDS

(57) Abstract: Novel methods of treating bone diseases or disorders are provided.

topical formulation contains suitably 0.01 to 5.0% of a compound of Formula (I). The active ingredient may be administered from 1 to 6 times per day, preferably once, sufficient to exhibit the desired activity, as is readily apparent to one skilled in the art.

- 5           As used herein, "treatment" of a disease includes, but is not limited to prevention, retardation and prophylaxis of the disease.

Diseases and disorders which might be treated or prevented, based upon the affected cells, include bone and mineral-related diseases or disorders; hypoparathyroidism; those of the central nervous system such as seizures, stroke,  
10 head trauma, spinal cord injury, hypoxia-induced nerve cell damage, such as occurs in cardiac arrest or neonatal distress, epilepsy, neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease, dementia, muscle tension, depression, anxiety, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, neuroleptic malignant syndrome, and  
15 Tourette's syndrome; diseases involving excess water reabsorption by the kidney, such as syndrome of inappropriate ADH secretion (SIADH), cirrhosis, congestive heart failure, and nephrosis; hypertension; preventing and/or decreasing renal toxicity from cationic antibiotics (*e.g.*, aminoglycoside antibiotics); gut motility disorders such as diarrhea and spastic colon; GI ulcer diseases; GI diseases with  
20 excessive calcium absorption such as sarcoidosis; autoimmune diseases and organ transplant rejection; squamous cell carcinoma; and pancreatitis.

In a preferred embodiment of the present invention, the present compounds are used to increase serum parathyroid ("PTH") levels in a non-pulsatile manner. Increasing serum PTH levels may be helpful in treating diseases such as  
25 hypoparathyroidism, osteosarcoma, periodontal disease, fracture, osteoarthritis, rheumatoid arthritis, Paget's disease and osteoporosis.

The normal range for intact PTH in humans is about 10 to about 65 pg/ml. Increasing serum PTH may also be useful to prophylactically retard or prevent the onset of a disease. Prophylactic treatment can be performed, for example, on a  
30 person with a low serum PTH, or a person without low serum PTH, but where increasing PTH has a beneficial compensating effect. Preferably, the patient has an

101  
0-2 PTH

*calcilytic compound  
is a compound able to  
inhibit CaR activity*

What is claimed is:

1. A method of treating a disease or disorder characterized by an abnormal bone or mineral homeostasis which comprises administering to a subject in need of treatment thereof an effective amount of a calcilytic compound in conjunction with an effective amount of an anti-resorptive agent.
2. A method according to claim 1 wherein the calcilytic compound is selected from the group consisting of:
  - N-[(2R-Hydroxy-3-[(3-chloro-2-cyano)phenoxy-propyl]-1,1-dimethyl-2-(2-naphthyl)ethyl amine hydrochloride;
  - N-[(2R-Hydroxy-3-[(3-chloro-2-cyano)phenoxy-propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl amine hydrochloride;
  - N-[(2R-Hydroxy-3-[(2,3-dichloro)phenoxy-propyl]-1,1-dimethyl-2-(4-methoxyphenyl)ethyl amine hydrochloride;
  - 15 N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-2-(6-(1,2,3,4-tetrahydronaphthyl)ethylamine;
  - N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-2-(Benzothien-3-yl)-ethylamine;
  - N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-2-(Benzothien-2-yl)-ethylamine;
  - 20 N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-2-(decahydronapthalen-2-yl)ethylamine;
  - N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-4-phenylbutylamine;
  - 25 N-[(R)-2-Hydroxy-3-[2-cyano-4-[N-methyl-N-[3-carboxyphenyl)sulfonyl]amino]-phenoxy]propyl]-1,1-dimethyl-4-(2-methoxyphenyl)butylamine;
  - N-[2R-Hydroxy-3-[[2-cyano-4-[N-methyl-N-[4-ethylcarboxyphenyl)sulfonyl]-amino]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine;
  - N-[2R-Hydroxy-3-[[2-cyano-4-[N-methyl-N-[3-
  - 30 methylcarboxymethoxyphenyl)sulfonyl]-amino]phenoxy]propyl]-1,1-dimethyl-2-(2-naphthyl)ethylamine;